NIH RELAIS Document Delivery

NIH-10099534

NIH -- W1 DE5083

PAMELA GEHRON ROBEY
CSDB/NIDR/NIH Bldng 30 Rm 228
30 CONVENT DRIVE MSC 4320
BETHESDA, MD 20892

ATTN:
PHONE: 301-496-4563
FAX: 301-402-0824
E-MAIL:

SUBMITTED: 2001-12-30 14:23:51
PRINTED: 2002-01-02 15:34:54
REQUEST NO.: NIH-10099534
SENT VIA: LOAN DOC
5394292

NIH Fiche to Paper Journal

TITLE:	DERMATOLOGY (BASEL, SWITZERLAND)
PUBLISHER/PLACE:	Karger Basel
VOLUME/ISSUE/PAGES:	1996;192(3):258-61 258-61
DATE:	1996
AUTHOR OF ARTICLE:	Schwartz RA; Spicer MS; Leevy CB; Ticker JB; Lambert WC
TITLE OF ARTICLE:	Cutaneous fibrous dysplasia: an incomplete form of
ISSN:	1018-8665
OTHER NOS/LETTERS:	Library reports holding volume or year 9203244 8726643
SOURCE:	PubMed
CALL NUMBER:	W1 DE5083
REQUESTER INFO:	AB424
DELIVERY:	E-mail: probey@DIR.NIDCR.NIH.GOV
REPLY:	Mail:

References

1 Mibelli V: Contribuzione allo studio della ipercheratosi dei canali sudoriferi. G Ital Mal Venerol 1893;28:313–355.
2 Chernosky ME, Freeman RG: Disseminated superficial actinic porokeratosis (DSAP). Arch Dermatol 1967;96:611–624.
3 Guss SB, Osbourn RA, Lutzner MA: Porokeratosis plantaris, palmaris et disseminata. A third type of porokeratosis. Arch Dermatol 1971;104:366–373.
4 Rahbari H, Cordero AA, Mehregan AH: Linear porokeratosis: A distinct clinical variant of porokeratosis of Mibelli. Arch Dermatol 1974;109:526–528.
5 Chernosky ME: Porokeratosis. Arch Dermatol 1986;122:869–870.
6 Adriaans B, Salisbury JR: Recurrent porokeratosis. Br J Dermatol 1991;124:383–386.
7 Eng AM: Wart-like porokeratosis of Mibelli. Acta Derm Venereol (Stockh) 1973;53:157–159.
8 Bacharach-Buhles M, Weindorf N, Altmeyer P: Porokeratosis Mibelli gigantea. Hautarzt 1990;41:633–635.
9 Otsuka F, Watanabe R, Kawashima W, Tomita Y, Ohara K, Ishibashi Y: Porokeratosis with large skin lesions. Histologic, cytologic and cytogenic study of three cases. Acta Derm Venereol (Stockh) 1991;71:437–440.
10 Mikhail GR, Wertheimer FW: Clinical variants of porokeratosis (Mibelli). Arch Dermatol 1968;98:124–131.
11 Degos R: Dermatologie. Paris, Flammarion, 1953, pp 669–669i.
12 Sato A, Böhm W, Bersch A: Hyperkeratotic form of porokeratosis Mibelli. Dermatologica 1977;155:340–349.
13 Marghescu S, Anton-Lamprecht I, Melz-Rothfuss B: Disseminated bilateral hyperkeratotic variant of porokeratosis Mibelli. Arch Dermatol Res 1987;279:39–47.
14 Jacyk WK, Esplin L: Hyperkeratotic form of porokeratosis of Mibelli. Int J Dermatol 1993;32:902–903.
15 Karnowsky MJ: A formaldehyde-glutaraldehyde fixative of high osmolality for use in electron microscopy. J Cell Biol 1965;27:137A–138A.
16 Jurecka W, Neumann RA, Knobler RM: Porokeratoses: Immunohistochemical, light and electron microscopic evaluation. J Am Acad Dermatol 1991;24:96–101.
17 Ito M, Fujiwara H, Maruyama T, Oguro K, Ishihara O, Sato Y: Morphogenesis of the cornoid lamella: Histochemical, immunohistochemical, and ultrastructural study of porokeratosis. J Cutan Pathol 1991;18:247–256.
18 Mann PR, Cort DF, Fairburn EA, Abdel-Aziz A: Ultrastructural studies on two cases of porokeratosis of Mibelli. Br J Dermatol 1974;90:607–617.

Dermatology 1996;192:258–261

Cutaneous Fibrous Dysplasia: An Incomplete Form of the McCune-Albright Syndrome

R.A. Schwartz
M.S. Spicer
C.B. Leevy
J.B. Ticker
W.C. Lambert

Dermatology and Pathology,
New Jersey Medical School, and the
Sammy Davis Jr. National Liver Institute,
Newark, N.J., USA

Abstract

A number of genetic disorders have been described in limited form. We report a patient with precocious puberty, large irregularly shaped café-au-lait spots since birth and a diffuse scalp alopecia showing the cutaneous changes of fibrous dysplasia. Histologically, the hair follicles were replaced by convolutions of fibrous tissue. This is to our knowledge the first patient reported with an apparently localized cutaneous form of this syndrome, a pattern predicted by the recently described somatic mutation of the $G_s\alpha$ gene. This is the second patient reported to our knowledge with the cutaneous McCune-Albright syndrome and scalp alopecia, and the first with diffuse scalp alopecia, the latter being the presenting sign. We believe that the differential diagnosis of both localized and diffuse alopecia should include the McCune-Albright syndrome.

Key Words

Cutaneous fibrous dysplasia
McCune-Albright syndrome
Scalp alopecia

In 1937, Albright et al. [1] described 5 women with a syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty. McCune [2] and McCune and Bruch [3] had described this disorder in a 9-year-old girl 1 year earlier. The McCune-Albright syndrome is now known to be a sporadic disorder whose manifestations may be explained by a somatic mutation of the $G_s\alpha$ gene [4, 5]. Scalp alopecia in this syndrome was described by Shelley and Wood [6]. This

Presented in part at the 32nd Annual Meeting, American Society of Dermatopathology, New Orleans, La., February 1–3, 1995, and published in abstract form [J Cutan Pathol 1995;22:85].

KARGER
E-Mail karger@karger.ch
Fax + 41 61 306 12 34

1018–8665/96/1923–0258 $ 10.00/0

Robert A. Schwartz, MD
New Jersey Medical School
University of Medicine and Dentistry of New Jersey
185 South Orange Avenue
Newark, NJ 07103-2714 (USA)

Received:
April 18, 1995
Accepted:
July 4, 1995

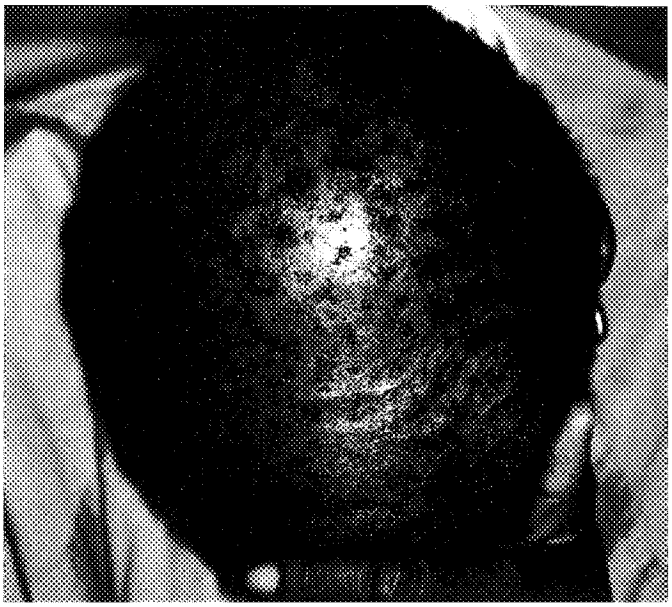

Fig. 1. Diffuse patchy alopecia of the scalp.

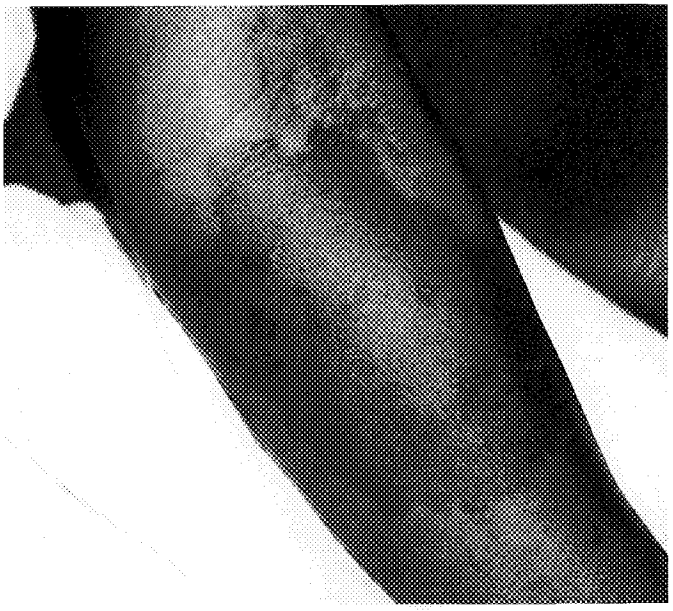

Fig. 2. Large café-au-lait patch on the left forearm.

is to our knowledge the first patient reported with the McCune-Albright syndrome presenting with diffuse alopecia of the scalp.

Case Report

A 52-year-old woman with primary biliary cirrhosis was evaluated for scalp alopecia. This patient described a history of onset of pruritus and progressive hair loss of the scalp and body of 4 years duration, with an associated generalized increase in pigmentation for the past 3 years. The alopecia began in the axilla and progressed to include the hair of her face, trunk and extremities. The loss on her scalp advanced rapidly, leaving sparse, thin hair. The hyperpigmentation was first noted on the dorsum of her feet but then generalized without association with solar exposure. Two large patches of hyperpigmentation on the left side of the abdomen and the left arm were related by the patient as birthmarks, having been present all of her life.

This woman subsequently developed pruritus and jaundice with associated dark urine and light, clay-colored stool. With the patient's main complaint of intractable pruritus, trials of plasmapheresis and antihistamines were carried out with little success. It was at this time that the patient was seen at our institution. The patient had had onset of menarche at the age of 9 years; she denied any history of bone fractures. Her medical history included diabetes mellitus which was treated with 40 units of NPH insulin each morning, left mastectomy for breast cancer in 1980 and cholelithiasis diagnosed by ultrasound in 1980. The family history was only significant for diabetes mellitus in her father. She had no known allergies to medications and denied cigarette smoking and alcohol use.

On physical examination, the patient was noted to have a well-developed body devoid of hair, but with scant patches on the scalp (fig. 1). On the left forearm, an 8×12 cm hyperpigmented patch with an irregular, jagged border was detected (fig. 2). A similar 10×15 cm hyperpigmented patch on the left side of her abdomen was also noted. Within these large hyperpigmented patches there were smaller, more deeply pigmented macules. No freckles or other pigmentation were present in the axillae, nor were any neurofibromas or xanthomas present. The sclerae were mildly icteric, the fundi showed sharp disk margins and no vascular changes, and the oral mucosa had two small pigmented areas. No palpable lymphadenopathy was noted, and the heart and lungs were normal. In addition, the abdominal examination showed a firm slightly enlarged, but nontender liver, with smooth margins measuring 16 cm in the midclavicular line. The spleen was not palpable. Musculoskeletal and neurological evaluation showed no abnormalities. The physical examination was otherwise unremarkable.

Initial laboratory findings included alkaline phosphatase, 1,210 U/l, alanine aminotransferase, 94 U/l, aspartate aminotransferase, 75 U/l, lactate dehydrogenase, 70 U/l, total bilirubin, 2.4 mg/dl, direct bilirubin, 1.3 mg/dl, albumin, 3.2 g/dl, prothrombin time, 12.0 s, cholesterol, 412 mg/dl and random glucose, 215 mg/dl. Her complete blood count revealed a hemoglobin level, 10.6 g/dl, hematocrit, 32.3%, white blood cell count, $3.4 \times 1{,}000/\mu l$, with a normal differential, platelet count, $174 \times 1{,}000/\mu l$ and a mean corpuscular volume, 72.2 μm^3. The electrolytes, blood urea nitrogen, creatinine, hepatitis A and B screens, serologic test for syphilis, thyroid studies, as well as iron, ferritin, total iron binding capacity, vitamin B_{12} and folic acid measurements were normal. Stool tested for occult blood was negative. A liver biopsy revealed expansion of the portal area with mononuclear cells, bile duct proliferation, lymphoid follicles and granulomas in the presence of fibrosis and lobular distortion compatible with the diagnosis of primary biliary cirrhosis. A repeat liver biopsy also demonstrated changes consistent with primary biliary cirrhosis of at least stage III. Antimitochondrial antibody and antinuclear antibody titers were within normal limits. Skeletal ra-

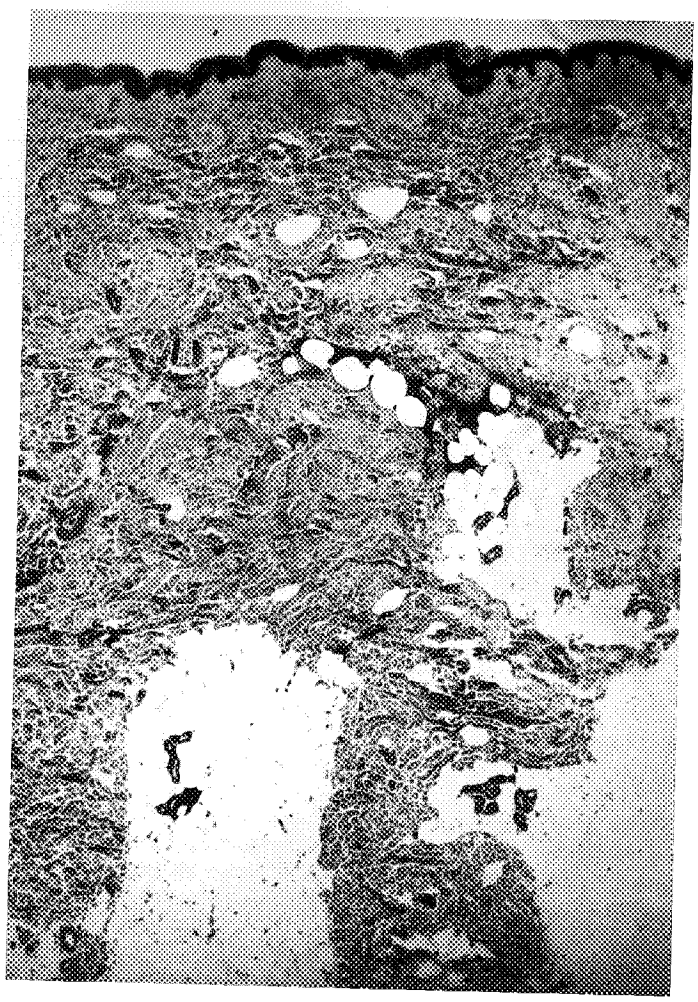

Fig. 3. Scalp skin showing complete replacement of dermal and deep follicular adnexal structures by fibrous tissue. Adipose tissue is found within the middermis. Note the remnant of pilar erector muscle in the upper middermis (center of photomicrograph). HE. × 10.

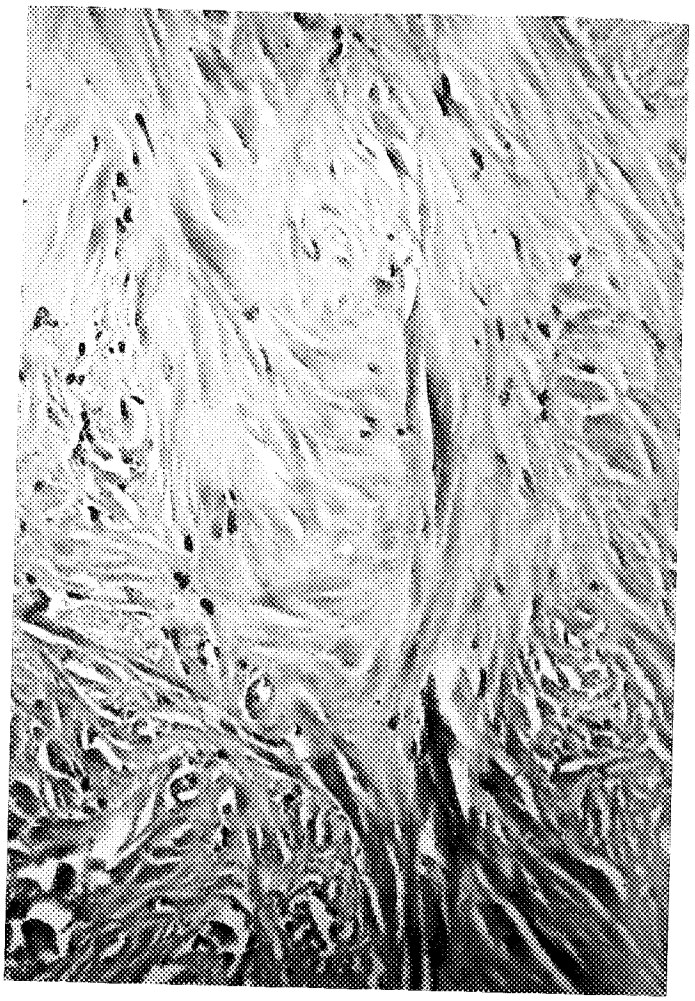

Fig. 4. Higher-power photomicrograph of a separate section showing a fibrinoid remnant of a hair follicle. HE. ×60.

diographs of the skull, chest and lower extremities revealed a normal bone cortex, and a bone scan showed no indication of fibrous dysplasia. Barium enema, esophagogastroduodensoscopy and colonoscopy were unable to detect any lesions or source of bleeding. Skin biopsy specimens of the scalp and the hyperpigmented lesion on the left arm were taken. There was no evidence in this patient of xanthelasma, sicca complex, Raynaud's phenomenon, CREST syndrome or Hashimoto's thyroiditis.

Therapy to address the intractable pruritus, including *d*-penicillamine, cholestyramine and phenobarbitol, have been unsuccessful. A liver transplant had been suggested, but the patient declined this treatment.

Histopathology

The microscopic findings of sections of the specimen from the hyperpigmented patch on the left arm, at multiple levels, demonstrated and increased prominence of melanocytes and melanin. This impression was consistent with the café-au-lait macule of Albright syndrome. Sections of the scalp revealed complete replacement of dermal and deep follicular adnexal structures by fibrous tissue. Adipose tissue was located within the middermis (fig. 3). The findings of fibrous dysplasia were noted in the hair follicles in several sections (fig. 4). Calcium was not evident in the dermis.

Discussion

The McCune-Albright syndrome appears to be the result of an early mutational event producing a mosaic population of cells, with the occurrence and degree of involvement in the skin, bone and endocrine tissues depending upon the number and location of cells bearing this mutation. To be more specific, original work found an early somatic mutation of the $G_s\alpha$ gene of endocrine organs with increased expression of the G_s protein [7, 8]. Recent studies have shown an activating $G_s\alpha$ mutation resulting in substitution of Arg with Cys or His at amino acid 201 of the $G_s\alpha$ protein. GTPase activity is inhibited causing an inappropriate stimulation of adenylyl cy-

clase. This has now been found in endocrine as well as nonendocrine tissue, specifically bone, of patients with McCune-Albright syndrome [4, 5]. Our patient's limited involvement seems to support this hypothesis.

The clinical manifestations of the somatic mutation of the $G_s\alpha$ gene are varied. The McCune-Albright syndrome is characterized by osteitis fibrosa disseminata, café-au-lait patches and sexual precocity. Other hyperfunctional endocrinopathies of the gonads, thyroid, adrenal cortex and pituitary somatotropes have been described [9]. Other nonendocrine manifestations of the McCune-Albright syndrome include hepatobiliary disease, cardiac disease and premature death [9]. The degree of involvement of each organ system ranges from severe, with neonatal death, to subtle. The latter may go undiagnosed.

The clinical features of café-au-lait macules found in Albright syndrome typically cover large areas of skin, are few in number and have the tendency to remain unilateral. The patches have a characteristic irregular border with serrated edges, resembling the 'coast of Maine' [6]. The café-au-lait macules of neurofibromatosis are found in greater number, usually 6 or more, and are smaller in size but exceeding 1.5 cm in diameter [10]. Moreover, the margins here tend to be smooth, with a likening to the coast of California. It has generally been recognized that these differences alone are not enough to distinguish these two diagnoses [11, 12].

Alopecia as a sign of the McCune-Albright syndrome was first described by Shelley and Wood [6]. They reported a 48-year-old woman with a circular patch of total alopecia of the right crown measuring 8 cm in diameter, which had been observed as a small patch enlarging since childhood. The histologic pattern was that not only of cutaneous fibrous dysplasia replacing hair follicles but also of ossification so remarkable that it was evident in soft tissue roentgenograms. Pierini et al. [13] also reported alopecia in a patient with McCune-Albright syndrome. The histology was consistent with nevus lipomatosus. The histology of the scalp specimen from our patient shows adipose tissue within the middermis. The significance of this is unclear; however, this may be another cutaneous manifestation of the somatic mutation of the $G_s\alpha$ gene. Our patient was unique in that the alopecia was so widespread as to involve the entire scalp. In addition, she lacked a history of either bone fractures or radiographic bone abnormalities. The lack of apparent fibrous dysplasia in bone is consistent with the somatic mutation hypothesis [4, 5, 7, 8] and represents to our knowledge the first patient with predominate cutaneous involvement. This is also the first time to our knowledge that primary biliary cirrhosis has been associated with this syndrome.

One should be aware that there are two clinically distinctive Albright syndromes, the McCune-Albright syndrome and Albright's hereditary osteodystrophy due to pseudohyperparathyroidism or to pseudopseudohyperparathyroidism [8, 14]. Cutaneous bone formation has been described in both syndromes [6, 14]. Both may be associated with defects in the $G_s\alpha$ gene [5, 15, 16]!

We report a case of diffuse, patchy alopecia as the presenting sign in a patient with McCune-Albright syndrome. The patient did not seek medical attention for her precocious puberty nor for her asymptomatic hyperpigmented café-au-lait patches. The lack of apparent fibrous dysplasia in bone is consistent with the somatic mutation hypothesis [4, 5, 7, 8]. We agree with Shelley and Wood [6] that the differential diagnosis of alopecia should include the McCune-Albright syndrome.

References

1 Albright F, Butler AM, Hampton AO, Smith P: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: Report of five cases. N Engl J Med 1937;216:727–746.

2 McCune DJ: Osteitis fibrosa cystica: The case of a nine-year-old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. Am J Dis Child 1936;52:743–744.

3 McCune DJ, Bruch H: Osteodystrophica fibrosa. Am J Dis Child 1937;54:806–848.

4 Malchoff CD, Reardon G, MacGillivray DC, et al: An unusual presentation of McCune-Albright syndrome confirmed by an activating mutation of the $G_s\alpha$-subunit from a bone lesion. J Clin Endocrinol Metab 1994;78: 803–806.

5 Shenker A, Weinstein LS, Sweet DE, et al: An activating $G_s\alpha$ mutation is present in fibrous dysplasia of bone in the McCune-Albright syndrome. J Clin Endocrinol Metab 1994;79:750–755.

6 Shelley WB, Wood MG: Alopecia with fibrous dysplasia and osteomas of skin: A sign of polyostotic fibrous dysplasia. Arch Dermatol 1976:112:715–719.

7 Weinstein LS, Shenker A, Gejman PV, et al: Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991;325:1688–1695.

8 Levine MA: The McCune-Albright syndrome: The whys and wherefores of abnormal signal transduction. N Engl J Med 1991;325: 1738–1740.

9 Shenker A, Weinstein LS, Moran A, et al: Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein G_s. J Pediatr 1993;123:509–518.

10 Crowe FW, Schull WJ: Diagnostic importance of café-au-lait spot in neurofibromatosis. Arch Intern Med 1953;91:758–766.

11 Benedict PH, Szabo G, Fitzpatrick TC, et al: Melanotic macules in Albright's syndrome and in neurofibromatosis. J Am Med Assoc 1968; 205:618–626.

12 Riccardi VM: Neurofibromatosis and Albright's syndrome. Dermatol Clin 1987;5: 193–203.

13 Pierini AM, Ortonne J-P, Floret D: Signes dermatologiques du syndrome de McCune-Albright. Ann Dermatol Vénéréol 1981;108: 969–976.

14 Eyre WG, Reed WB: Albright's hereditary osteodystrophy with cutaneous bone formation. Arch Dermatol 1971;104:635–642.

15 Patten JL, Johns DR, Valle D, et al: Mutation in the gene encoding the stimulatory G protein of adenylate cyclase in Albright's hereditary osteodystrophy. N Engl J Med 1990;322: 1412–1419.

16 Miric A, Vechio JD, Levine MA: Heterogenous mutations in the gene encoding the alpha-subunit of the stimulatory G protein of adenylyl cyclase in Albright hereditary osteodystrophy. J Clin Endocrinol Metab 1993; 76:1560–1568.